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Original Article

Predictors of treatment failure following early antibiotic discontinuation in culture-negative, ventilator-associated pneumonia: an observational study

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Abstract

Introduction: Early antibiotic discontinuation in clinically suspected ventilator-associated pneumonia (VAP) may lead to infection relapse/recurrence and increase mortality. This study aimed to evaluate the incidence and potential predictors of treatment failure with this approach.

Methodology: A retrospective observational study was conducted between September 2014 and November 2016 in a mixed intensive care unit. We included clinically suspected VAP patients whose quantitative sputum cultures from endotracheal aspirate were negative, allowing antibiotic discontinuation within 24 hours. Patients were monitored for signs and symptoms of recurrent VAP. Incidence and risk factors for treatment failure, defined as pneumonia recurrence, were determined using univariate logistic regression analysis and receiver operating characteristic (ROC) curves.

Results: Forty-three patients met the inclusion criteria. The incidence of treatment failure among culture-negative VAP following early antibiotic discontinuation was 27.9% (12 patients). There were no significant differences in procalcitonin levels, leukocyte counts or body temperature between the two groups, except for the modified clinical pulmonary infection score (mCPIS) (5.42 ± 2.19 versus 3.9 ± 1.54, p = 0.014). Procalcitonin levels at VAP diagnosis and antibiotic cessation both showed low predictive capacity for treatment failure (AUC 0.56, CI 95% 0.36–0.76 and AUC 0.57, CI 95% 0.37–0.76, respectively). However, combining mCPIS with procalcitonin improved the predictive value for treatment failure (AUC 0.765, CI 95% 0.56–0.96).

Conclusions: Early antibiotic discontinuation may lead to a high incidence of treatment failure among culture-negative VAP patients. Procalcitonin alone should not guide antibiotic discontinuation decisions while combining mCPIS and procalcitonin enhances predictive accuracy for treatment failure.

Key words: Early antibiotic discontinuation; negative culture; VAP; procalcitonin; clinical pulmonary infection score.

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Introduction

Ventilator-Associated Pneumonia (VAP) occurs in up to one-third of all mechanically ventilated patients in intensive care unit (ICU) and contributes significantly to healthcare costs, morbidity and mortality [1]. Once clinical suspicion is established, effective broad-spectrum antibiotics are the mainstay of treatment. This is followed by a de-escalation strategy to reduce prolonged antibiotic exposure [2]. This antibiotic stewardship strategy has been proven to reduce antibiotic use and prevent the emergence of highly resistant pathogens without increasing recurrent infection and mortality [3,4]. While it is crucial to obtain reliable microbiological evidence and a susceptibility profile to guide further antibiotics therapy, pathogenic organisms may not be identified in the sputum cultures of 50%-60% of VAP patients [5,6].

The American Thoracic Society/ Infectious Disease Society of America (ATS/IDSA) guidelines suggest that antibiotics be withheld if there is clinical improvement in patients with suspected VAP whose quantitative culture results are below the diagnostic threshold for VAP [2,7]. A study by Yamana *et al.* revealed that de-escalation therapy did not affect mortality in community-acquired pneumonia patients whose sputum cultures were negative but increased mortality of patients with extremely severe pneumonia from 2.9% to 17.9% [8]. Moreover, switching from broad-spectrum intravenous to oral antibiotics in patients with hospital-acquired pneumonia was associated with 10.3% lower mortality, as shown in the study by Buckel *et al.* [9]. Noteworthy non-de-escalation patients had higher criteria for severe pneumonia. Outside patient mortality, recurrent infection remains the most feared complication when deciding to discontinue antibiotics. In VAP with negative culture, recurrent pneumonia occurred in 5.9% to 28.6% depending on early or late antibiotic discontinuation [10,11].

Pro-calcitonin (PCT) is a well-known predictor for outcomes in sepsis [12,13]; however, its diagnostic value is less clear in nosocomial infections such as VAP. ATS/IDSA guidelines suggest using PCT + clinical criteria to guide antibiotic discontinuation; however, whether the benefits exist in patients with a therapy duration of less than seven days is uncertain [2].

Early de-escalation has been recommended at 48-72 hours following the antibiotic administration if the clinical course is favorable and quantitative sputum culture results are negative [1]. Even though it is controversial, this strategy might help reduce antibiotic-related adverse effects such as resistance or *Clostridium difficile* emergence, especially in patients with prior antibiotic exposure [1]. We are unaware of any study exploring the predictive role of PCT for treatment failure after early antibiotic discontinuation in culture-negative VAP. This study aimed to identify the incidence and potential predictors of treatment failure after discontinuing antibiotics in VAP patients with negative sputum culture.

Methodology

Study design and definitions

This was a retrospective observational study conducted at a general/mixed ICU of the University medical center (UMC) in Ho Chi Minh City (HCMC), Vietnam.

Inclusion criteria

Patients who fulfilled all the criteria were enrolled. These criteria were: (1) ≥ 18 years old, (2) clinically suspected VAP according to ATS/IDSA guidelines as the presence of new lung infiltrate + clinical evidence, which includes the new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation, (3) negative sputum culture, (4) attending physicians decided to discontinue antibiotics within 24 hours after receiving negative sputum culture and witnessing clinical improvement that includes no worsening of oxygenation, the highest temperature of less than 38.5 °C, and leukocyte count of greater than 4 g/L and less than 10 g/L, (5) PCT test was done on the day of VAP diagnosis. The study site institution has neither official indications for testing PCT nor standard protocols for antibiotic de-escalation.

Exclusion criteria

Patients with immunosuppression and concomitant infection from other sites that prevented antibiotic discontinuation were excluded from this study. Immunosuppression was defined as one of the following: systemic corticosteroid exposure for > 5 days within 30 days prior to admission, cancer patient who received chemotherapy within 45 days prior to admission, HIV, neutrophil of < 500/μL, and organ transplant patients on immunosuppressive therapy. Additionally, patients in whom endotracheal aspirate could not be obtained after antibiotic discontinuation were excluded.

Failure of early antibiotic discontinuation

De-escalation was considered early when the patient with negative sputum culture was withdrawn from all antibiotics within 24 hours of culture report finalization. The treatment was considered a failure when the patients developed (1) leukocytes > 10×10^9/L, or (2) had a new infiltrate or progression of an existing infiltrate on chest radiograph, accompanied by the quantitative sputum samples within 48 hours of antibiotics discontinuation being positive with pathogens that were not sensitive to previously prescribed antibiotics. The treatment failure required the modification of antibiotic therapy.

Microscopy of sputum and pro-calcitonin test

Sputum samples were obtained by endotracheal aspirate and quantitatively cultured. Sputum culture was considered negative according to the criteria of our institute's Microbiology Department, which are as follows: (1) < 10^4 colonies/mL, (2) normal respiratory flora, and (3) non-pathogenic organisms, e.g., *Candida*, *Enterococcus*. The decision to obtain serial PCTs was at the attending physicians' discretion. Patients with VAP underwent PCT tests at least on the days of VAP diagnosis and antibiotic discontinuation. PCT tests were performed using a COBAS machine (Roche, Germany).

Data collection

Age, sex, acute physiology, and chronic health evaluation II (APACHE II) scores at ICU admission, mCPIS at VAP diagnosis, mechanical ventilation (MV) indications, antibiotic prescribed before sputum culture, duration of MV, ICU length of stay, hospital length of stay, PCTs at the time of VAP diagnosis and antibiotic discontinuation, body temperature and white blood cells at antibiotic discontinuation, the incidence of recurrent VAP and mortality were recorded using a collection data sheet. Since all enrolled patients had negative sputum cultures, we modified the CPIS in which sputum culture criteria were omitted to evaluate the risk of pneumonia. A new score was developed for better predicting recurrent VAP by combining mCPIS

Table 1. Patient characteristics according to outcomes of early antibiotic discontinuation.

	Overall (N = 43)	Success (N = 31)	Failure (N = 12)	*p* value
Age (years)	76 (65-84.5)	74 (65-83.5)	81 (68-86)	0.498
APACHE II	18 ± 4.86	17.87 ± 4.65	18.50 ± 5.57	0.709
Antibiotic therapy prior to sputum culture (n, %)	18 (41.9%)	13 (41.9%)	5 (41.7%)	1
Comorbidity (n, %)				
Neurologic disease	13 (30.2%)	8 (25.8%)	5 (41.7%)	0.828
COPD	12 (27.9%)	9 (29%)	3 (25%)	
Cardiovascular disease	14 (32.5%)	10 (32.3%)	4 (33.3%)	
Post-operative respiratory failure	3	3 (9.7%)	0	
Acute liver failure	1	1 (3.2%)	0	
Body Temperature on antibiotic cessation (°C)	37 (37-37.5)	37 (37-37.45)	37 (37-37.58)	0.41
Leukocyte on antibiotic cessation (G/L)	12.1 ± 4.07	11.69 ± 4.19	13.10 ± 3.71	0.313
Antibiotic duration	3 (3-3)	3 (3-3)	3 (3-3)	0.87
PCT on VAP diagnosis (ng/mL)	1.45 (0.35-4.02)	1.13 (0.37-3.38)	1.84 (0.36-4.62)	0.551
PCT on antibiotic cessation (ng/mL)	0.3 (0.16-0.7)	0.28 (0.15-0.71)	0.30 (0.19-0.89)	0.49
mCPIS	4 (1-9)	3.9 ± 1.54	5.42 ± 2.19	0.014
mCPIS + PCT	4.84 ± 1.91	4.35 ± 1.58	6.08 ± 2.19	0.006
Mortality (n, %)	8 (18.6%)	5 (16.1%)	3 (25%)	0.665

Data were presented as mean ± standard deviation, median (interquartile range) and n, %. COPD: chronic obstructive pulmonary disease; APACHE II: Acute Physiology and Chronic Health Evaluation; mCPIS: modified clinical Pulmonary Infection Score; VAP: ventilator-associated pneumonia; PCT: procalcitonin.

and PCT on the day of antibiotic discontinuation. The incorporated score was interpreted as follows: either two points or one point was added to mCPIS if PCT was ≥ 1ng/mL or ≥ 0.5 ng/mL, respectively. The mCPIS remained the same if PCT was < 0.5 ng/mL. The fundamental for adding points to mCPIS is the result of the univariate logistic regression model in which the odd ratios of PCT ≥ 1ng/mL and PCT ≥ 0.5 ng/mL in predicting recurrent VAP were 2.25 and 1.4, respectively.

Statistical analysis

Categorical variables were presented as frequencies or percentages and were compared using Chi-squared tests, or Fisher's exact test when appropriate. Normally distributed and non-normally distributed variables were reported as mean ± standard deviation (SD) and median ± interquartile range (25%-75%), respectively. Continuous variables were compared by Student t test or Mann-Whitney test when appropriate. Correlations between risk factors and recurrent VAP were assessed by logistic regression analysis. Logistic regression analysis was also used to test the discriminating capacity of a model including mCPIS and PCT for recurrent VAP. Receiver operating characteristic (ROC) curves were calculated to test the accuracy of PCT, mCPIS, and mCPIS + PCT in predicting recurrent VAP. The optimal cut-off values were determined by the Youden method. A p value ≤ 0.05 was considered statistically significant. All data were analyzed using R 3.5.1 software.

Ethics

The Ethics Committee of the University of Medicine and Pharmacy at HCMC approved the study protocol (ethical approval number 34A/ĐHYD-HĐ) and waived the need for documented written consent because both patients were unable to provide direct consent given their illness and the decision to discontinue antibiotics is traditionally at the attending doctor's discretion. However, the patient's next of kin were informed about the study and were given the right to withdraw the patient from the study.

Results

Description of the population

Between September 2014 and November 2016, 646 patients diagnosed with VAP were screened in the ICU of the University Medical Center, Ho Chi Minh City (Figure 1). A total of 43 patients who met the criteria were included in the study. The median age was 76 years, with males accounting for more than 60%.

Figure 1. Flow chart of patient selection.

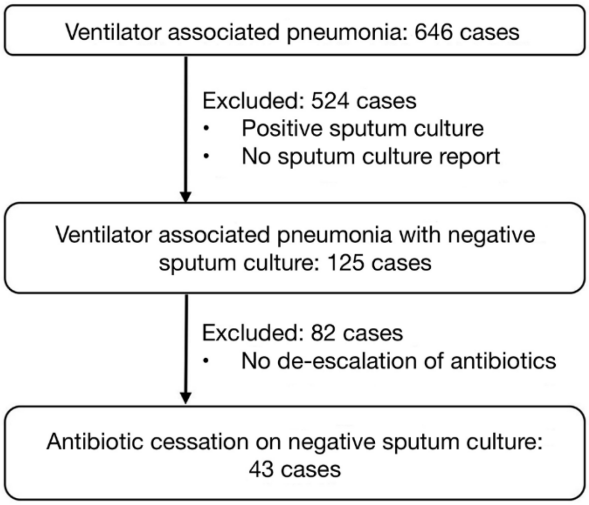

Table 2. Summary of antibiotic therapy.

Antibiotic	Number of patients treated
Carbapenem	35
Betalactam	5
Piperacillin-tazobactam	3
Quinolone	29
Amikacin	2
Vancomycin	3
Linezolid	1
Teicoplanin	4
Clindamicin	2

Antibiotic combinations: carbapenem + quinolone 22 cases, betalactam + quinolone 1 case, piper/tazo 1 case, carbapenem 3 cases, piper/tazo + quinolone 1 case, carbapenem + vancomycin 1 case, carbapenem + amikacin + linezolid 1 case, carbapenem + teicoplanin 2 cases, carbapenem + quinolone + vancomycin 2 cases, piper/tazo + quinolone + teico 1 case, carbapenem + amikacin 1 case, betalactam 2 cases, carbapenem + clindamycin 2 cases, betalactam + clindamycin 1 case, carbapenem + quinolone + teicoplanin 1 case, ceftriaxone + quinolone 1 case.

Cardiovascular disease, neurological disease, and chronic obstructive pulmonary disease (COPD) were frequent indications for mechanical ventilation. Other indications included post-operative respiratory failure and acute liver failure. Although pneumonia was not present at the onset of mechanical ventilation, systemic antibiotics were administered for other reasons in 18 patients (41.9%). Empiric antibiotics were administered for three days in 35 patients, four days in five patients, and five days in three patients. Empiric therapy consisted of a carbapenem or antipseudomonal cephalosporin + fluoroquinolone or aminoglycoside. Vancomycin or Teicoplanin was added in four patients. Table 1 describes the characteristics of patients enrolled in the study, and the combination of antibiotics is summarized in Table 2.

Forty-eight hours after antibiotic cessation, treatment failure was recorded in 12 patients, accounting for 27.9%. Repeated sputum culture revealed that most isolated pathogens were non-fermenting gram-negative bacteria and *Staphylococcus aureus* (Table 3). Pneumonia due to multiple pathogens was reported in two patients.

Table 3. Isolated pathogens in repeated sputum culture.

Pathogen	Number of times pathogens isolated
Acinetobacter baumanii	5
Klebsiella pneumonia	3
Pseudomonas aeruginosa	3
Escherichia coli	1
Staphylococcus aureus	2

Comparison between patients with and without treatment failure

Table 1 compares the characteristics of patients with treatment failure and treatment success. The median age of those in the failure group was higher ($p = 0.49$). Additionally, patients in the failure group were mechanically ventilated largely due to neurological disease compared to the other group; however, the difference was not statistically significant ($p = 0.8$). The most noticeable discrepancy was the mCPIS at VAP diagnosis in the failure group which was higher than the success group (student t-test, 5.42 (2.19) vs 3.9 (1.54), $p = 0.014$). A non-significant trend toward higher PCT values on both days of VAP diagnosis and antibiotic cessation was shown in patients in the failure group ($p = 0.55$ and $p = 0.49$, respectively). No significant differences were found in the body temperature and serum leukocytes on the day of antibiotic cessation ($p = 0.41$ and $p = 0.31$, respectively).

Comparison between patients with and without prior antibiotic exposure

There were 18 patients who previously received antibiotics for different reasons. The median duration of exposure was four days. There were no differences in the two groups regarding comorbidities ($p = 0.885$),

Table 4. Patient characteristics according to prior antibiotic exposure.

	No exposure (N = 25)	Prior exposure (N = 18)	*p* value
Age	74 (68-85)	78.50 (61.5-83.75)	0.873
APACHE II	16.72 ± 5.14	19.89 ± 3.88	0.033
Duration of antibiotic exposure	0 (0-0)	4 (2-6)	< 0.001
Comorbidity (n, %)			
Neurologic disease	7 (28%)	6 (33.3%)	0.885
COPD	7 (28%)	5 (27.8%)	
Cardiovascular disease	9 (36%)	5 (27.8%)	
Post-operative respiratory failure	2 (8%)	1 (5.6%)	
Acute liver failure	0 (0%)	1 (5.6%)	
Body Temperature on antibiotic cessation (°C)	37 (37-37)	37.35 (37-37.77)	0.025
Leukocyte on antibiotic cessation (G/L)	11.65 ± 4.06	12.70 ± 4.13	0.410
PCT on VAP diagnosis (ng/mL)	0.83 (0.26-2.47)	1.94 (1.11-4.55)	0.044
PCT on antibiotic cessation (ng/mL)	0.20 (0.13-0.34)	0.47 (0.24-1.08)	0.013
mCPIS	4.20 ± 1.71	4.50 ± 2.07	0.605
mCPIS + PCT	4.52 ± 1.83	5.28 ± 1.99	0.204
Treatment failure (n, %)	7 (28%)	5 (27.8%)	1.00
Mortality (n, %)	4 (16%)	4 (22.2%)	0.701

Data were presented as mean ± standard deviation, median (interquartile range), and n, %. COPD: chronic obstructive pulmonary disease; APACHE II: Acute Physiology and Chronic Health Evaluation; mCPIS: modified clinical Pulmonary Infection Score; VAP: ventilator-associated pneumonia; PCT: procalcitonin.

Table 5. Predictors of recurrent ventilator-associated pneumonia among 43 participants, using logistic regression model.

	Odd ratio	95% confidence interval	*p* value
Temperature	0.82	0.27 – 2.44	0.72
Leukocyte	1.09	0.92 – 1.29	0.31
PCT	1.38	0.63 – 3.06	0.42
PCT > 0.25 ng/mL	1.15	0.3 – 4.44	0.84
PCT > 0.5 ng/mL	1.5	0.38 – 5.92	0.56
PCT > 1 ng/mL	2.25	0.42 – 12.03	0.34
mCPIS	1.66	1.07 – 2.59	0.02
mCPIS + PCT	1.77	1.13 – 2.8	0.01

mCPIS: modified clinical Pulmonary Infection Score; PCT: procalcitonin.

leukocyte ($p = 0.41$), mCPIS ($p = 0.6$), treatment failure rate ($p = 1$), and mortality ($p = 0.7$). The exposure group had a higher severity score (APACHE II of 19.89 versus 16.72, $p = 0.03$), statistically but non-clinically higher body temperature (37.25 versus 37, $p = 0.025$), higher procalcitonin at VAP diagnosis and antibiotic cessation ($p = 0.04$ and $p = 0.01$, respectively). Table 4 summarizes the characteristics of these two groups.

Predictors of treatment failure

Of all parameters recorded on the days of VAP diagnosis and antibiotic cessation, body temperature, serum leukocytes, and serum PCT at both time points were not associated with failed antibiotic discontinuation. The mCPIS and a combination of mCPIS and serum PCT on antibiotic cessation were associated with treatment failure with OR of 1.66 (CI 95% 1.07 – 2.59) and 1.77 (CI 95% 1.13 – 2.8), respectively (Table 5).

Table 6 and Figure 2 show the diagnostic value and optimal cut-off of mCPIS and serum PCT in predicting failure following antibiotic discontinuation. Among the parameters recorded on the day of VAP diagnosis, serum PCT had low diagnostic capacity to differentiate failure and success after antibiotic discontinuation, assessed by the area under the ROC curve, AUC 0.56 (CI 95% 0.36 – 0.76). The optimal cut-off of ≥ 1.37 ng/mL provided positive predictive value of 34.8% and negative predictive value of 80%. The mCPIS for VAP diagnosis had better discriminative capacity with AUC 0.715 (CI 95% 0.52 – 0.92). The optimal cut-off of ≥ 5 yielded a positive predictive value of 44.4% and negative predictive value of 84%. The combination of mCPIS and serum PCT improved the diagnostic value of recurrent VAP with AUC 0.765 (CI 95% 0.56 – 0.96). The optimal cut-off of ≥ 6 resulted in a positive predictive value of 53% and a negative predictive value of 88.5% (Figure 2).

Other parameters on the day of antibiotic discontinuation, including temperature and serum leukocyte count, both had inadequate capacity to predict failure after antibiotic cessation.

Discussion

Although the current guidelines for VAP treatment recommend de-escalation of antibiotics in mechanically ventilated patients, antibiotic de-escalation in sputum culture-negative patients remains controversial. This study shows that among 43 VAP patients in whom antibiotics were discontinued on negative sputum

Figure 2. Predictive capacity of PCT and PCT + mCPIS for treatment failure.

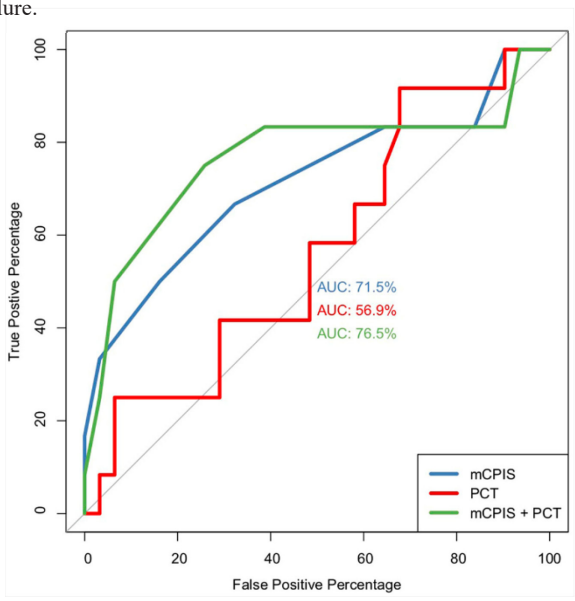

Table 6. Diagnostic value of PCT, mCPIS for recurrent VAP compared with other parameters.

	Cut-off	AUC	Sens	Spec	PPV	NPV
Temperature (°C)	≥ 37.8	0.575 (0.37-0.78)	25%	84%	37.5%	74.3%
Leukocyte (G/L)	≥ 13.4	0.616 (0.43-0.80)	58.3%	67.7%	41.2%	80.8%
PCT on VAP diagnosis (ng/mL)	≥ 1.37	0.56 (0.36-0.76)	66.7%	51.6%	34.8%	80%
PCT on antibiotic cessation (ng/mL)	≥ 0.17	0.57 (0.37-0.76)	91.6%	32.2%	34.4%	91%
mCPIS	≥ 5	0.715 (0.52-0.91)	66.7%	67.7%	44.4%	84%
mCPIS + PCT	≥ 6	0.765 (0.56-0.96)	75%	74.2%	53%	88.5%

AUC: area under the ROC curve; PPV: positive predictive value; NPV: negative predictive value; Sens: sensitivity; Spec: specificity.

culture, more than twenty-five percent were reported as failure and required antibiotic resume despite satisfactory clinical condition at the time of cessation. The recurrent infection can explain the high rate of failure following antibiotic discontinuation in this study. Recurrent infection can be defined as relapse when the subsequent pathogens are the same as the initial pathogens and superinfection when different pathogens are present [14]. Since the initial sputum samples were negative in our study, we could not precisely identify relapse and superinfection following antibiotic discontinuation. The first study of sputum culture-negative VAP showed that the incidence of recurrent VAP was 5.9% among 101 recruited patients who had a mean CPIS of 6.3 ± 0.7 [11]. Another study showed that recurrent VAP incidence was approximately 10% if antibiotics were discontinued immediately on negative sputum cultures but increased to 28.6% if antibiotics were stopped later [10]. In a more recent study, discontinuation of empiric anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agent resulted in no difference in 28-day mortality; however, mortality in the de-escalation group was quite high, up to 23% [15]. To our knowledge, in addition to the disease severity and prolonged length of stay, there may be some other, unknown reasons contributing to the high incidence of unsuccessful antibiotic discontinuation seen in our study.

First, the sputum-obtaining technique used in this study was endotracheal aspiration, which, according to ATS/IDSA, can be used for VAP screening because of its high sensitivity, but does not provide high accuracy. In mechanically ventilated patients, tracheal aspiration had sensitivity ranging from 73% to 86% compared to the gold standard, quantitative bronchoscopy culture [16]. Furthermore, in newly intubated community-acquired pneumonia patients, 27% of patients revealed negative sputum culture on endotracheal aspiration despite positive blood culture or positive urinary antigen for *Pneumococcus* or *Legionella* [17]. Second, the administration of antibiotics before sputum culture partly contributed to the increase in false negative-sputum culture results. The insufficient duration of antibiotic therapy may contribute to the persistent infection, explaining the reuse of antibiotics. A study assessing the impact of antibiotic usage on sputum culture showed that the rate of positive culture gradually decreased, in order, from the no antimicrobial therapy group to recent and current antimicrobial treatment groups (86%, 68%, and 42%, respectively) [18]. Another study showed that among the culture-positive VAP patients, 21.6% of previous positive samples became negative after six hours, and this rate continued to rise at 12 and 24 hours, particularly in samples with gram-negative bacteria [19]. In our study, more than 40% of patients enrolled were exposed to antibiotics previously administered for other indications, possibly leading to a false negative-sputum culture which only became positive after antibiotic discontinuation (persistent VAP). Noticeably, most isolated pathogens post-cessation were non-fermenting Gram-negative bacilli and *Staphylococcus aureus*, which are known as recurrent VAP-causative pathogens even with appropriate antibiotic treatment [20]. Third, it is possible that recurrent ventilator-associated trachea-bronchitis rather than pneumonia developed in some patients in the failure group [21]. Although the first negative sputum culture does not clarify that the pathogens isolated in the second culture are responsible for the former VAP or simply superimposed, the results of our study, in part, emphasize the cautious approach in interpreting the sputum culture of a patient with prior antibiotic therapy.

One of the most common challenges in the diagnosis of VAP is accuracy, as no gold standard investigation exists. Traditionally, VAP is confirmed based on quantitative sputum culture, though this remains a contentious issue [2]. As such, a negative sputum culture makes it more difficult to establish the diagnosis. In a cohort of the patients suspected of VAP, mean serum PCT in VAP patients confirmed by bronchoalveolar lavage was significantly higher than that in non-VAP patients (0.94 ± 2.37 μg/L versus 0.34 ± 1.48 μg/L); however, there was a remarkable overlap in PCT levels between two groups and the diagnostic capacity of PCT for VAP was just moderate with AUC of 0.68 [22]. Luyt *et al.* [5] also showed that the most recommended level of PCT (≥ 0.5 ng/mL) for VAP diagnosis had the sensitivity and specificity of 72% and 24%, respectively. There are very few studies exploring the role of PCT in the guidance of antibiotic discontinuation [23]. Previous studies showed that PCT combined with CPIS helped guide antibiotic discontinuation and reduce therapy duration. None of these studies focused on the culture-negative population [24,25]. Although only culture-negative patients were enrolled in the present study, the serum PCT level on the day of VAP diagnosis was higher than that in the comparative study by Povoa *et al.* [22]; however, there also was a significant overlap in PCT levels between failed and successful antibiotic discontinuation groups, making PCT a poor indicator of de-escalation. Given the contribution of several underlying diseases to the systemic inflammatory reaction in critical care patients,

PCT plays a limited role in predicting recurrent infection.

The CPIS including clinical parameters and sputum cultures was introduced by Pugin and had a sensitivity of 93% and a specificity of 100% in VAP diagnosis [26]. A follow-up meta-analysis showed that CPIS had moderate accuracy in VAP diagnosis when the VAP incidence was low, resulting in an increase in false positive [27]. Simplified CPIS is predictable of recurrent infection following PCT-guided antibiotic discontinuation in VAP [14]. Our study was conducted in culture-negative patients, and the attending physicians stopped antibiotics only with stable clinical conditions. These resulted in marginal mCPIS; however, it is the best index per se to predict treatment failure and subsequent antibiotic reescalation with both sensitivity and specificity of approximately 67%. In this challenging scenario, the combination of a clinical score (mCPIS) and a biomarker (PCT) helped, in part, improve the predictive capacity for failed antibiotics discontinuation, predominantly in the negative predictive value aspect. This combination has a major advantage in excluding treatment failure, thereby restricting unnecessary prolonged antibiotic use with little risk of under-treatment.

Several limitations of our study should be noted. First, our sample size was small and the duration of the study was prolonged because of different practices in antibiotic discontinuation. Most attending physicians did not discontinue antibiotics despite negative sputum culture, particularly when the clinical condition of the patient was unstable. Second, nearly half of the enrolled patients were exposed to prior antibiotics, causing a great impact on sputum culture results. Too short a course of antibiotics may be inadequate and increase the risk of persistent infection which, in turn, may explain a high rate of treatment failure. Worthy of note is that despite higher severity scores, patients with prior antibiotic exposure had similar rates of treatment failure and death to the unexposed groups in the present study (Table 4). Furthermore, prior antibiotic exposure makes it challenging to attribute treatment failure to relapse or superimposed infection. Further studies should be conducted to investigate the efficacy of early antibiotic discontinuation in patients without prior antibiotic exposure. Last, investigators were not equipped to obtain sputum by invasive bronchoscopy at the time of the study, which may have improved the diagnostic accuracy of VAP.

Conclusions

Our study suggests that early antibiotic discontinuation is rarely performed in clinically suspected VAP patients with negative sputum culture and may result in a high rate of treatment failure. In these patients, the combination of mCPIS and PCT, not PCT alone, might help in determining the appropriate time of antibiotic discontinuation.

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References

1. Papazian L, Klompas M, Luyt CE (2020) Ventilator-associated pneumonia in adults: a narrative review. Intensive Care Med 46: 888–906. doi: 10.1007/s00134-020-05980-0
2. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, Napolitano LM, O'Grady NP, Bartlett JG, Carratalà J, El Solh AA, Ewig S, Fey PD, File TM Jr, Restrepo MI, Roberts JA, Waterer GW, Cruse P, Knight SL, Brozek JL (2016) Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the infectious diseases society of America and the American thoracic society. Clin Infect Dis 63: e61–e111. doi: 10.1093/cid/ciw353
3. Ohji G, Doi A, Yamamoto S, Iwata K (2016) Is de-escalation of antimicrobials effective? A systematic review and meta-analysis. Int J Infect Dis 49: 71–9. doi: 10.1016/j.ijid.2016.06.002
4. Eachempati SR, Hydo LJ, Shou J, Barie PS (2009) Does de-escalation of antibiotic therapy for ventilator-associated pneumonia affect the likelihood of recurrent pneumonia or mortality in critically ill surgical patients? J Trauma 66: 1343–8. doi: 10.1097/TA.0b013e31819dca4e
5. Luyt CE, Combes A, Reynaud C, Hekimian G, Nieszkowska A, Tonnellier M, Aubry A, Trouillet JL, Bernard M, Chastre J (2008) Usefulness of procalcitonin for the diagnosis of ventilator-associated pneumonia. Intensive Care Med 34: 1434–40. doi: 10.1007/s00134-008-1112-x
6. Kollef MH, Morrow LE, Niederman MS, Leeper KV, Anzueto A, Benz-Scott L, Rodino FJ (2006) Clinical characteristics and treatment patterns among patients with ventilator-associated pneumonia. Chest 129: 1210–8. doi: 10.1378/chest.129.5.1210
7. Dellit TH, Owens RC, McGowan JE, Gerding DN, Weinstein RA, Burke JP, Huskins WC, Paterson DL, Fishman NO, Carpenter CF, Brennan PJ, Billeter M, Hooton TM (2007) Infectious diseases society of america and the society for healthcare epidemiology of america guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 44: 159–177. doi: 10.1086/510393
8. Yamana H, Matsui H, Tagami T, Hirashima J, Fushimi K, Yasunaga H (2016) De-escalation versus continuation of empirical antimicrobial therapy in community-acquired pneumonia. J Infect 73: 314–25. doi: 10.1016/j.jinf.2016.07.001
9. Buckel WR, Stenehjem E, Sorensen J, Dean N, Webb B (2017) Broad- versus narrow-spectrum oral antibiotic transition and outcomes in health care-associated pneumonia. Ann Am Thorac Soc 14: 200–205. doi: 10.1513/AnnalsATS.201606-486BC

10. Raman K, Nailor MD, Nicolau DP, Aslanzadeh J, Nadeau M, Kuti JL (2013) Early antibiotic discontinuation in patients with clinically suspected ventilator-associated pneumonia and negative quantitative bronchoscopy cultures. Crit Care Med 41: 656–63. doi: 10.1097/CCM.0b013e318287f713
11. Kollef MH, Kollef KE (2005) Antibiotic utilization and outcomes for patients with clinically suspected ventilator-associated pneumonia and negative quantitative BAL culture results. Chest 128: 2706–13. doi: 10.1378/chest.128.4.2706
12. Schuetz P, Birkhahn R, Sherwin R, Jones AE, Singer A, Kline JA, Runyon MS, Self WH, Courtney DM, Nowak RM, Gaieski DF, Ebmeyer S, Johannes S, Wiemer JC, Schwabe A, Shapiro NI (2017) Serial Procalcitonin predicts mortality in severe sepsis patients: results from the multicenter procalcitonin MOnitoring SEpsis (MOSES) study. Crit Care Med 45: 781–789. doi: 10.1097/ccm.0000000000002321
13. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P (2013) Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis 13: 426–35. doi: 10.1016/s1473-3099(12)70323-7
14. Wang Q, Hou D, Wang J, An K, Han C, Wang C (2019) Procalcitonin-guided antibiotic discontinuation in ventilator-associated pneumonia: a prospective observational study. Infect Drug Resist 12: 815–824. doi: 10.2147/idr.s190859
15. Cowley MC, Ritchie DJ, Hampton N, Kollef MH, Micek ST (2019) Outcomes associated with de-escalating therapy for methicillin-resistant staphylococcus aureus in culture-negative nosocomial pneumonia. Chest 155: 53–59. doi: 10.1016/j.chest.2018.10.014
16. Scholte JB, van Dessel HA, Linssen CF, Bergmans DC, Savelkoul PH, Roekaerts PM, van Mook WN (2014) Endotracheal aspirate and bronchoalveolar lavage fluid analysis: interchangeable diagnostic modalities in suspected ventilator-associated pneumonia? J Clin Microbiol 52: 3597–604. doi: 10.1128/jcm.01494-14
17. McCauley LM, Webb BJ, Sorensen J, Dean NC (2016) Use of tracheal aspirate culture in newly intubated patients with community-onset pneumonia. Ann Am Thorac Soc 13: 376–81. doi: 10.1513/AnnalsATS.201506-368BC
18. Llitjos J-F, Amara M, Benzarti A, Lacave G, Bedos J-P, Pangon B (2018) Prior antimicrobial therapy duration influences causative pathogens identification in ventilator-associated pneumonia. J Crit Care 43: 375–377. doi: 10.1016/j.jcrc.2017.10.027
19. Byrnes MC, Irwin E, Reicks P, Brodsky I (2013) Prospective, protocolized study evaluating effects of antibiotics on sputum culture results in injured patients. Surg Infect 14: 24–29. doi: 10.1089/sur.2012.022
20. Combes A, Luyt C-E, Fagon J-Y, Wolff M, Trouillet J-L, Chastre J, for the PTG (2007) Early predictors for infection recurrence and death in patients with ventilator-associated pneumonia. Crit Care Med 35: 146-54. doi: 10.1097/01.CCM.0000249826.81273.E4
21. Chastre J, Luyt C-E (2016) Does this patient have VAP? Intensive Care Med 42: 1159–1163. doi: 10.1007/s00134-016-4239-1
22. Póvoa P, Martin-Loeches I, Ramirez P, Bos LD, Esperatti M, Silvestre J, Gili G, Goma G, Berlanga E, Espasa M, Gonçalves E, Torres A, Artigas A (2016) Biomarker kinetics in the prediction of VAP diagnosis: results from the BioVAP study. Ann Intensive Care 6: 32. doi: 10.1186/s13613-016-0134-8
23. Alessandri F, Pugliese F, Angeletti S, Ciccozzi M, Russo A, Mastroianni CM, d'Ettorre G, Venditti M, Ceccarelli G (2021) Procalcitonin in the assessment of ventilator associated pneumonia: a systematic review. Adv Exp Med Biol 1323: 103–114. doi: 10.1007/5584_2020_591
24. Wongsurakiat P, Tulatamakit S (2018) Clinical pulmonary infection score and a spot serum procalcitonin level to guide discontinuation of antibiotics in ventilator-associated pneumonia: a study in a single institution with high prevalence of nonfermentative Gram-negative bacilli infection. Ther Adv Respir Dis 12: 1753466618760134. doi: 10.1177/1753466618760134
25. Beye F, Vigneron C, Dargent A, Prin S, Andreu P, Large A, Quenot JP, Bador J, Bruyere R, Charles PE (2019) Adhering to the procalcitonin algorithm allows antibiotic therapy to be shortened in patients with ventilator-associated pneumonia. J Crit Care 53: 125–131. doi: 10.1016/j.jcrc.2019.05.022
26. Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew PD, Suter PM (1991) Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. Am Rev Respir Dis 143: 1121–9. doi: 10.1164/ajrccm/143.5_Pt_1.1121
27. Shan J, Chen HL, Zhu JH (2011) Diagnostic accuracy of clinical pulmonary infection score for ventilator-associated pneumonia: a meta-analysis. Respir Care 56: 1087. doi: 10.4187/respcare.01097.

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